

being obvious over U.S. Patent No. 3,764,692 (Lowenstein) in view of U.S. Patent No. 5,536,516 (Moffett, et al.) and McCarty (45 Medical Hypotheses 247-54 (1995)).

In an Advisory Action mailed on September 22, 2000, the Examiner stated that Applicants amendments and response filed on September 5, 2000 would not be entered because Applicant failed to provide a copy of the Bruengraber, et al. article, upon which Applicant's response was based in part.

Responsive to the Office action dated June 28, 2000, Applicant hereby cancels claims 32-39 without prejudice, and replaces them with new claims 40 and 41 provided herein, and traverses the Examiner's rejections of Applicant's claims. In addition, Applicant hereby includes a copy of the Bruengraber, et al. article with this petition.

The Examiner concedes that Lowenstein and Moffett do not teach the use of (-)hydroxycitric acid (HCA) for increasing athletic endurance. The Examiner alleges, however, that McCarty shows that HCA can be administered to increase exercise endurance. The Examiner argues that McCarty's hypotheses is backed by strong reasoning based on the literature in the art, and provides a strong enough case for one skilled in the art to expect that HCA would increase exercise endurance. The Examiner also dismisses the Dohm reference because it does not mention HCA.

Applicants respectfully disagree with this interpretation of McCarty and Dohm.

McCarty's hypothesis is that because HCA, by inhibiting citrate lyase, reduces the generation of acetyl CoA in the liver, the reduced acetyl CoA complements the ability of glucagon to promote gluconeogenesis. McCarty further hypothesizes that glycogen is accumulated in the liver and this accumulation *may* aid aerobic endurance.

Dohm, however, teaches that increased fatty acid utilization, which results from lower glycogen levels in the liver, promotes aerobic endurance. Thus, although Applicant agrees that one skilled in the art could imagine that promoting gluconeogenesis may enhance exercise endurance, Dohm teaches that McCarty's hypothesis is groundless. The fact that Dohm does not mention HCA is irrelevant to Dohm's conclusion.

Applicants note McCarty's selective use of references, in particular Brunengraber, et al., 82 Eur. J. Biochem. 373-84 (1978), cited as Reference No. 48 by McCarty. This paper shows that the administration of HCA to livers of fed rats increased the concentrations of the glycolytic intermediates glucose 6-phosphate and fructose 6-phosphate, while decreasing the concentrations of all other intermediates. These results are convincing because HCA, by promoting the accumulation of citric acid, inhibits the enzyme phosphofructokinase. Thus, any glucose produced by the action of HCA will not enter into the TCA cycle via glycolysis due to the inhibition of phosphofructokinase by HCA. Therefore, even if glucose is produced by gluconeogenesis, that glucose is not available as an energy source and cannot enhance exercise endurance. Those skilled in the art of biochemistry will realize that McCarty focuses only on one aspect of the function of HCA, and that his arguments are speculative. McCarty's paper is based on an incomplete understanding of the functioning of HCA, and would not teach one skilled in the art to reasonably expect that HCA would increase exercise endurance. One of ordinary skill in the art therefore would not be motivated to use the HCA compositions taught by the Lowenstein and Moffett et al. patents in the method taught by McCarty.

Applicant also submits a Declaration under 37 C.F.R. 1.132 of Dr. Tohru Fushiki, one of the inventors of the present application, in response to the Examiner's comments regarding the published articles by M. F. McCarty, Inhibition of Citrate Lyase May Aid Aerobic Endurance, 45 Medical Hypotheses, 247-54 (1995); and G. Lynis Dohm et al., Influence of Fasting on Glycogen Depletion in Rats During Exercise, 55 (3) J. Applied Physiology: Respirat. Environ. Exercise Physiol. 830-33 (1983). Dr. Fushiki's curriculum vitae is included with the Declaration.

Thus, in view of Dr. Fushiki's Declaration and the above remarks, Applicants urge that claims 24-31 are not obvious in light of Lowenstein, Moffett, and McCarty, and respectfully request reconsideration and withdrawal of this rejection.

Claims 32-39 were rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 3,764,692 (Lowenstein) in view of U.S. Patent No. 5,536,516 (Moffett, et al.) and McCarty (45 Medical Hypotheses 247-54 (1995)).

The Examiner argued that food is a pharmaceutically acceptable carrier and that it is obvious to mix a pharmaceutical with food.

Applicant has canceled claims 32-39 and added claims 40-41 reciting food as a limitation on the composition of claims 24-25. Claims 40-41 are dependent on claims 24-25, and are therefore allowable for at least the reasons that claims 24-25 are allowable. Reconsideration and withdrawal of this rejection is respectfully requested.

It is submitted that claims 24-31, as amended, and new claims 40-41 are in condition for allowance. Early and favorable action by the Examiner is earnestly solicited. If the Examiner believes that issues may be resolved by a telephone interview, the Examiner is respectfully urged to telephone the undersigned at (212) 848-1046. The undersigned may also be contacted by e-mail at erzucidlo@gj.com.


AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for this amendment, or credit any overpayment to Deposit Account No. 50-1561.

Respectfully submitted,

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Date: May 10, 2001

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CERTIFICATE OF MAILING

This is to certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Assistant Commissioner for Patents, Washington, D.C. 20231, on May 10, 2001.

Eugene C. Rzucidlo
Name of applicant, assignee
Or registered representative


Signature

May 10, 2001
Date of Signature



In re Application of: Tohru Fushiki et al

DATE:

U.S. Serial No.: 09/367,481

ART UNIT: 1651

FILED: August 13, 1999

Examiner: Coe, S.

FOR: ATHLETIC ENDURANCE INCREASING AGENT

DECLARATION OF TOHRU FUSHIKI, PH.D.

I, Tohru Fushiki, Ph.D., declare that:

1. I am one of the inventors of the invention in U.S. Patent Application No. 09/367,481.
2. I received an undergraduate degree from the Faculty of Agriculture at Kyoto University in 1974.
3. I received a doctorate in agriculture at the Graduate School of Kyoto University in 1979.
4. I became an Assistant of nutritional chemistry in 1979 and was promoted to Assistant Professor in 1988.
5. Since 1994 I have been a Professor of nutritional chemistry at Kyoto University.
6. I am the principal author or co-author of approximately 90 publications in nutritional chemistry. A complete curriculum vitae is enclosed as Exhibit A.
7. I am aware of what constitutes ordinary skill in the art and knowledge in the art in biochemistry, and in particular, as it relates to nutritional chemistry. I closely

and carefully follow the scientific literature regarding development of special foods to increase endurance capacity.

8. I am submitting this declaration to respond to the Examiner's comments regarding the published articles by M. F. McCarty, Inhibition of Citrate Lyase May Aid Aerobic Endurance, 45 Medical Hypotheses, 247-54 (1995); and G. Lynis Dohm et al., Influence of Fasting on Glycogen Depletion in Rats During Exercise, 55 (3) J. Applied Physiology: Respirat. Environ. Exercise Physiol. 830-33 (1983).

9. The Examiner reasoned that while McCarty's hypotheses (though unsupported by scientific data) were well-reasoned and therefore credible, the article by Dohm is not entirely pertinent as prior art since it makes no mention of (-) hydrocitric acid (HCA) in his experiments (Office Action, June 28, 2000 ¶5).

10. I respectfully disagree. The article by Dohm clearly presents sufficient data for a person of ordinary skill in the biochemical arts to conclude that increased endurance of fasted rats is likely to be the result of increased fatty acid oxidation and the sparing of muscle glycogen.

11. Dohm teaches that fasting increases fatty acid utilization and is accompanied by a concomitant decrease in carbohydrate utilization in rats during exercise. This increase in fatty acid oxidation elevates the concentrations of Acetyl-CoA and citrate, which in turn reduces the activities of phosphofructokinase and pyruvate dehydrogenase. The reduced activities of these enzymes result in decreased glucose utilization.

12. At the time of the invention, HCA was known in the art to inhibit citrate lyase, the enzyme which cleaves citrate during glycolysis. The link between glycolysis and the citric acid cycle is the oxidative decarboxylation of pyruvate to form acetyl CoA..

13. At the time of the invention, HCA also was known in the art to inhibit lipid synthesis via its inhibition of ATP citrate lyase. See McCarty at 250 (citing Henri Brunengraber, et al., Fatty Acid 3- β -Hydroxysterol And Ketone Synthesis In The Perfused Rat Liver, 82 Eur. J. Biochem. 373-84 (1978)). HCA does so by inhibiting the utilization of Acetyl Co A as a carbon source in the synthesis of long chain fatty acids.

14. At the time of the invention, HCA was known in the art to promote glycogen synthesis and thereby causes accumulation of glycogen in the liver. Glycogen is known as a storage form of glucose in the liver. The hormone glucagon is known in the art to elicit the breakdown of glycogen by the liver. During normal muscular activity, the liver releases glucose into the blood. During prolonged exercise, glucagon also promotes fatty acid oxidation.

15. McCarty's article hypothesizes that (1) HCA reduces the generation of acetyl CoA in the liver by inhibiting citrate lyase; (2) this reduced acetyl CoA complements the ability of glucagon to promote gluconeogenesis; and (3) the accumulation of glycogen in the liver may aid aerobic endurance.

16. I am of the opinion that McCarty's paper would not have led a person of ordinary skill in the biochemical arts to reasonably expect that HCA would enhance aerobic endurance because the article's theories are based on an incomplete understanding of how HCA functions.

17. Although I agree that one of ordinary skill in the art could envision that promoting gluconeogenesis may enhance exercise endurance, Dohm teaches that McCarty's hypothesis is groundless. Lower glycogen levels in the liver, not the increased glycogen levels hypothesized by McCarty, enhance aerobic endurance.

18. Furthermore, Brungraber's paper teaches that the administration of HCA to livers of fed rats increases the concentrations of glycolytic intermediates glucose-6-phosphate and fructose 6-phosphate while decreasing the concentrations of all other intermediates.

20. Brungraber's results are consistent with what is known in the art regarding HCA's inhibition of the enzyme phosphofructokinase. Phosphofructokinase is the key enzyme in the control of glycolysis. A high level of ATP inhibits phosphofructokinase by decreasing its affinity for fructose-6-phosphate. Citrate enhances the inhibitory effect of ATP.

21. HCA inhibits phosphofructokinase by promoting the accumulation of citric acid. This inhibition prevents any glucose produced by the action of HCA from entering into the citric acid cycle via glycolysis.

22. Thus even if glucose is produced during gluconeogenesis, it is not available as an energy source and cannot enhance exercise endurance.

23. I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Respectfully submitted,

By 
Dr. Tohru Fushiki

Tohru Fushiki, Ph.D.

EDUCATION:

- 1979 Kyoto University, Graduate School
 Doctorate in Agriculture
- 1974 Kyoto University
 Undergraduate degree in Agriculture

ACADEMIC EXPERIENCE:

- 1994 to present Kyoto University
 Professor, Nutritional Chemistry
- 1988 Kyoto University
 Assistant Professor, Nutritional Chemistry
- 1979 Kyoto University
 Assistant, Nutritional Chemistry

RESEARCH ACTIVITIES (1997-2001):

- Functional design of high acceptability in food resources;
- Recognition of foods in the small intestinal cells;
- Development of special foods to increase endurance capacity;
- Regulational factors of adipocyte proliferation and differentiation in response to food intake;
- Mechanism of generation of feelings of fatigue in brain after exercise.

PUBLICATIONS (1994-2001):

Original Papers:

Takeda M, Imaizumi M, Sawano S, Manabe Y, Fushiki T. Long-Term Optional Ingestion Of Corn Oil Induces Excessive Caloric Intake And Obesity In Mice. *Nutrition.*, **17** 117-120 (2001).

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